SYNTHESIS OF SUBSTANCES EFFECTING ON C.N.S. VI

Synthesis and Previous Pharmacological Examinations of Ketoxime Isomer—Pairs

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During our earlier synthetic examinations efforts have been made to separate some syn- and anti-isomers of piperidine-ketoximes. This paper presents the separation of ketoxime-isomers and their informing pharmacological investigations.

Generally in the literature, of the aldoxime and ketoxime isomers is described either alone the more stabile or the mixture of the syn- and anti-oximes.

VARGHA, OCSKAY [1, 2] treated the production and separation of the various furyl-ketoxime-pairs and the determination of their configuration. The general and the above mentioned anthors' experience is in most of the cases the m. p. of anti-isomer is higher that is the most stabile form and the syn-isomer can be produced from the anti-isomer with dry etheric-HCl or with HCl-gas. These authors could demonstrate differences also in the UV-spectrum of the ketoxime-isomer-pairs [1].

Several γ-aminoketones were prepared to the synthesis of *p*-alkyl-aryl-propene-derivatives [3] and so in many cases there was a possibility to prepare the oxime isomer pairs. FOULHOUX [4] observed that the monoizonitroso-acetone possesses strong antinicotine activity [4]. So in the case of some amino-ketones oxime-isomer pairs were prepared in order to be able to examine the eventual difference observable between their pharmacological activity and to connect it with the chemical structure.

Our further aim is to prepare to investigate the complex-forming properties of oxime isomers and to reveal its UV-spectrum further to synthetize their various derivatives such as acetate and tosylate, *etc.*

The ketoximes where prepared in alkalic conditions when taking into consideration the mechanism suggested by INGOLD [5].

$$NH_2.OH + OH^{(-)} = NH^{(-)}.OH + H_2O$$

$$R.\overset{\overset{O}{\|}}{C}.CH_2.CH_2.N.R_1R_2 + NH_2.O^{(-)}$$

$$R.C.(CH_2)_2.N.R_1R_2$$

$$^{(-)}O \quad NH.OH$$

$$+H_2O$$

$$R.C.(CH_2)_2.N.R_1R_2 + OH^{(-)}$$

$$HO \quad NH.OH$$

$$-H_2O$$

$$R.C.(CH_2)_2.N.R_1R_2 + OH^{(-)}$$

$$\overset{\overset{NOH}{\|}}{C}$$

I and II isomer pairs are existing:

$$R.\overset{\overset{N.OH}{\|}}{C}.(CH_2)_2.N.R_1R_2 \qquad I = \text{R-anti-ketoxime}$$

$$R.\overset{\overset{HO.N}{\|}}{C}.(CH_2)_2.N.R_1R_2 \qquad II = \text{R-syn-ketoxime}$$

When I and II subjected to BECKMANN-rearrangement and hydrolysis the following derivatives can be expected in I:

$$R{\cdot}NH_2 + HO_2C{\cdot}(CH_2)_2{\cdot}N{\cdot}R_1R_2$$

whereas in II:

$$H_2N{\cdot}(CH_2)_2{\cdot}N{\cdot}R_1R_2 + HO_2C{\cdot}R$$

as it is generally known in BECKMANN-rearrangement always the group in the anti-position is shifted.

Carrying out SCHMIDT reaction the following two products (A, B) were obtained in the case of 1-piperidino-3-phenyl-propanone-3 examined [6] and produced also by us

$$C_6H_5.\overset{\overset{O}{|}}{C}.NH.(CH_2)_2.N\,C_5H_{10} \qquad \text{A.,}$$

$$C_6H_5.NH.\overset{\overset{O}{\|}}{C}.(CH_2)_2.N\,C_5H_{10} \qquad \text{B.,}$$

Having hydrolised the substances A, B we obtained the designated products.

The structure of syn- and anti-oxime isomers can, be studied with FÖLDI's complex forming method [7].

We could demonstrate a difference in pharmacological activity between the two 1-piperidino-3-phenyl-propanone-3-oxim-isomers, inasmuch as the anti-isomer of a higher m. p. showed in a smaller dose a higher antinicotinic activity than the syn-pair.

Experimental:

1-piperidino-3-phenyl-propanon-3-(I).

Substance I was obtained from piperidine-HCl, paraformaldehyde and acetophenone with Mannich-condensation. [8].

1-piperidino-3-phenyl-propanone-oxime-3-HCl (II, III).

It was produced with different methods and in spite of different circumstances always obtained, the presumable R-anti-oxime with the higher m. p. (II).

Two typical examples:

20% hydroxilamine-HCl excess later $NH_2OH \cdot HCl$ is added to the 100 ml ethanol solution of 15,3 g I. and refluxed in water bath for 3 hours. Then filter it hot and evaporate the alcohol at atmospherical pressure and dry with benzene ethanol azeotrop. Dissolving the substance in abs. acetone 12 g of crystalline substance is obtained.

M. p.: 89—90 °C.

The substance is extremely hygroscopic.

It can be well solved in benzene, methanol, ethanol and butanol; while in acetone very poorly, if cold it is not solving in ether and ethylate all, heated it slowly solves in latter two cases. Recrystallized from ethanol, acetone (1:2) mixture an other product is separated its m. p. 177 °C.

This is likely the R-anti-modification (II). Solving substance II in dry MeOH streaming it HCl-gas with cooling (9) quantitatively a substance of lower m. p. is produced.

M. p.: 128—130 °C.

Presumably this will be an other isomer (R-syn modification) III. The analysis of both substances is in good agreement with the oxime-hydrochlorides (Tabl. I).

(The physico-chemical and analytical data of the substances are shown in Table I.)

The oxime is prepared with an other method with $NH_2OH \cdot HCl$ and $NaHCO_3$ in aqueous MeOH: 5 g substance I is solved in 50 ml of MeOH and adding the solution of 2,2 g $NaHCO_3$ in 15 ml of distilled water and 1,8 g of $NH_2OH \cdot HCl$. Refluxed it in water bath for 2 hours and after distilled the solvent. The residue is suspended in water and extract it with ether. Drying (Na_2SO_4 sicc.), filtering and evaporating, small white crystalls are obtained.

M. p.: 107—109 °C, presumably it is a mixture of two isomers, which during the recrystallization becomes the stable isomer (II).

After streaming dry HCl gas through its solution can be turned substance III, too.

Table 1

Name of the substances		Summary form	M. w.	Physical data	ANALYSIS								
					Calculated				Found				
					C	H	N	Cl	C	H	N	Cl
α-1-piperidino-3-phenyl-propanone-3-oxime	HCl	$C_{14}H_{21}N_2OCl$	263	mp.:177 °C	68,87	9,64	10,65	13,31	68,7	9,60	10,47	13,2
β-1-pipereidino-3-phenyl-propanone-3-oxime	HCl	$C_{14}H_{21}N_2OCl$	263	mp.:128—130 °C	68,87	9,64	10,65	13,31	68,80	9,47	10,80	13,6
α-1-piperidino-acetopheno-neoxime	HCl	$C_{12}H_{19}N_2OCl$	249	mp.:136 °C	62,6	5,62	11,24	10,04	62,6	5,2	11,0	9,6
β-1-piperidino-acetopheno-neoxime	HCl	$C_{13}H_{19}N_2OCl$	249	mp.:118—120 °C	62,6	5,62	11,24	10,04	62,4	5,4	11,6	9,8
α-1-N-piperidino-butanone-3-oxime	HCl	$C_9H_{19}N_2OCl$	206	mp.:194—198 °C	52,4	9,23	13,6	17,0	51,65	9,32	13,70	17,20
β-1-N-piperidino-butanone-3-oxime	HCl	$C_9H_{19}N_2OCl$	206	mp.:150—152 °C	52,4	9,23	13,6	17,0	51,95	9,2	13,72	17,30

ω-piperidino-acetophenone (IV) (10).

Substance IV was obtained by condensing ω-bromo-acetophenone and piperidine.

ω-piperidino-acetophenone-oxime (V, VI) (11).

Oxime V was prepared from HCl of substance IV.

M. p.: 118—120 °C.

Solving oxime V in abs. MeOH and bubbling dry HCl-gas through the solution the HCl salt of the other oxime-isomer is obtained (VI).

M. p.: 190 °C.

The m. p. of oxime-VI 135—137 °C (11), which can be obtained by fractionated crystallization of isomer V from MeOH.

1-N-piperidino-3-butanone (VII) (12).

It was prepared from piperidine-HCl, paraformaldehyde and acetone.

1-N-piperidino-3-butanon-oxime (VIII).

10 g of ketone (VII) is solved in 35 ml of abs. EtOH and 4,5 g of $NH_2OH \cdot HCl$ and 5,47 g dry NaOAc is added to it. Refluxed in water bath for 5 hours. The hot solution is filtered. Evaporated it white precipitate occurs m. p.: 165—170 °C. Recrystallized from MeOH m. p.: 150—152 °C. (Table 1.)

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ИЗУЧЕНИЕ ДЕЙСТВИЯ МЕЖДУ ФИЗИОЛОГИЧЕСКИМИ И ХИМИЧЕСКИМИ СРОЕНИЯМИ ВЕЩЕСТВ, ДЕЙСТВУЮЩИХ НА ЦЕНТРАЛЬНЫЙ НЕРВНЫЙ МОЗГ. VI

Синтез измерных пар кетоксима и их фартакологическов рассмотрение

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Уже раньше удалось приготовить изомерную пару многих пиперидин-кетоксима. Публикация занимается изготовлением изомеров кетоксима и их предворительными фармакологическими рассмотрениями.

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